

CLAIMS

1. A MHC Class I-restricted epitope peptide derived from survivin, said epitope having at
5 least one of the following characteristics:
 - (i) capable of binding to the Class I HLA molecule to which it is restricted at an affinity as measured by the amount of the peptide that is capable of half maximal recovery of the Class I HLA molecule (C_{50} value) which is at the most 50 μ M as determined by the assem-
10 bly binding assay as described herein,
 - (ii) capable of eliciting INF- γ -producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10^4 PBLs as determined by an ELISPOT assay, and/or
 - 15 (iii) capable of *in situ* detection in a tumor tissue of CTLs that are reactive with the epitope peptide.
2. A peptide according to claim 1 having a C_{50} value, which is at the most 30 μ M.
- 20 3. A peptide according to claim 2 having a C_{50} value, which is at the most 20 μ M.
4. A peptide according to claim 1, which is restricted by a MHC Class I HLA-A molecule.
5. A peptide according to claim 4, which is restricted by a MHC Class I HLA species se-
25 lected from the group consisting of HLA-A1, HLA-A2, HLA-A3, HLA-A11 and HLA-A24.
6. A peptide according to claim 5, which is restricted by HLA-A2.
7. A peptide according to claim 6, which is selected from the group consisting of
30 FLKLDREIRA (SEQ ID NO:1), TLPPAWQPFL (SEQ ID NO:2), ELTLGEFLKL (SEQ ID NO:3),
LLLGEFLKL (SEQ ID NO:4) and LMLGEFLKL (SEQ ID NO:5).
8. A peptide according to claim 1, which is restricted by a MHC Class I HLA-B molecule.
- 35 9. A peptide according to claim 8, which is restricted by a MHC Class I HLA-B species se-
lected from the group consisting of HLA-B7, HLA -B35, HLA -B44, HLA-B8, HLA-B15, HLA-
B27 and HLA-B51.
10. A peptide according to claim 9, which is restricted by HLA-B35.
- 40 11. A peptide according to claim 10, which is selected from the group consisting of
CPTENEPDL (SEQ ID NO:6), EPDLAQCFY (SEQ ID NO:7), CPTENEPDY (SEQ ID NO:8) and
EPDLAQCFY (SEQ ID NO:9).

12. A peptide according to claim 1 comprising at the most 20 amino acid residues.
13. A peptide according to claim 12 that comprises at the most 10 amino acid residues.
- 5 14. A peptide according to claim 1, which is a nonapeptide or a decapeptide.
15. A peptide according to claim 1, which is a native sequence of survivin of a mammal species.
- 10 16. A peptide according to claim 15 that is derived from human survivin.
17. A peptide according to claim 1, which is derived from a native sequence of survivin by substituting, deleting or adding at least one amino acid residue.
- 15 18. A peptide according to any of the preceding claims, which is phosphorylated.
19. A peptide according to claim 18, which comprises Thr34 of the native survivin disclosed in US 6.245.523.
- 20 20. A peptide according to claim 1 comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table:

HLA allele	Position 1	Position 2	Position 3	Position 5	Position 6	Position 7	C-terminal
HLA-A1		T,S	D,E			L	Y
HLA-A2		L, M			V		L,V
HLA-A3		L,V,M	F,Y				K, Y, F
HLA-A11		V,I,F,Y	M,L,F,Y,I				K, R
HLA-A23		I,Y					W,I
HLA-A24		Y		I,V	F		I,L,F
HLA-A25		M,A,T	I				W
HLA-A26	E,D	V,T,I,L,F			I,L,V		Y,F
HLA-A28	E,D	V,A,L					A,R
HLA-A29		E					Y,L
HLA-A30		Y,L,F,V					Y
HLA-A31			L,M,F,Y				R
HLA-A32		I,L					W
HLA-A33		Y,I,L,V					R
HLA-A34		V,L					R
HLA-A66	E,D	T,V					R,K
HLA-A68	E,D	T,V					R,K
HLA-A69		V,T,A					V,L
HLA-A74		T					V,L
HLA-B5		A,P	F,Y				I,L

HLA-B7	P				L,F
HLA-B8		K	K,R		L
HLA-B14	R,K				L,V
HLA-B15 (B62)	Q,L,K,P, H,V,I,M, S,T				F,Y,W
HLA-B17					L,V
HLA-B27	R				Y, K,F,L
HLA-B35	P				I, L, M, Y
HLA-B37	D,E				I,L,M
HLA-B38	H	D,E			F,L
HLA-B39	R,H				L,F
HLA-B40 (B60,61)	E	F,I,V			L,V,A,W, M,T,R
HLA-B42	L,P				Y,L
HLA-B44	E				F,Y,W
HLA-B46	M,I,L,V				Y,F
HLA-B48	Q,K				L
HLA-B51	A,P,G				F,Y,I,V
HLA-B52	Q	F,Y			I,V
HLA-B53	P				W,F,L
HLA-B54	P				
HLA-B55	P				A,V
HLA-B56	P				A,V
HLA-B57	A,T,S				F,W,Y
HLA-B58	A,T,S				F,W,Y
HLA-B67	P				L
HLA-B73	R				P
HLA- Cw1	A,L				L
HLA- Cw2	A,L				F,Y
HLA- Cw3	A,L				L,M
HLA- Cw4	Y,P,F				L,M,F,Y
HLA- Cw6					L,I,V,Y
HLA- Cw6	Y				L,Y,F
HLA- Cw8	Y				L,I,
HLA- Cw16	A,L				L,V

21. A peptide according to claims 1 that is capable of eliciting INF- γ -producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 10⁴ PBLs.
- 5 22. A peptide according to claim 1, which is capable of eliciting INF- γ -producing cells in a PBL population of a patient having a cancer disease where survivin is expressed.
23. A peptide according to claim 22 where the cancer disease is selected from the group consisting of a haematopoietic malignancy including chronic lymphatic leukemia and
 10 chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer, lung cancer, colon cancer, pancreas cancer and prostate cancer.
24. A peptide according to claim 1, which is capable of eliciting INF- γ -producing cells in a PBL population of a patient having a cancer disease, said INF- γ -producing cells having cy-
 15 tototoxic effect against survivin expressing cells of a cancer cell line, including a cell line selected from the group consisting of the breast cancer cell line MCF-7 and the melanoma cell line FM3.
25. A pharmaceutical composition comprising the peptide according to claim 1.
- 20 26. A composition according to claim 25 that comprises a peptide according to claim 4 in combination with a peptide according to claim 8.
27. A composition according to claim 26 comprising a peptide according to claim 6 in combination with a peptide according to claim 10.
- 25 28. A composition according to claim 25, which is a vaccine capable of eliciting an immune response against a cancer disease.
- 30 29. A composition according to claim 25, further comprising an immunogenic protein or peptide fragment selected from a protein or peptide fragment not belonging to or derived from the survivin protein family.
30. A composition according to claim 29, where the protein or peptide fragment not
 35 belonging to or derived from the survivin protein family is a protein, or peptide fragment hereof, involved in regulation of cell apoptosis.
31. A composition according to claim 29 where the immunogenic protein or peptide fragment selected from a protein or peptide fragment hereof not belonging to or derived
 40 from the survivin protein family is Bcl-2 or a peptide fragment hereof.
32. A composition according to claim 25, which is a multiepitope vaccine.

33. A composition according to claim 28 where the vaccine is capable of eliciting an immune response against a cancer disease where survivin is expressed.
34. A composition according to claim 33 where the cancer disease is selected from the
 5 group consisting of a haematopoietic malignancy including chronic lymphatic leukemia and chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer, lung cancer, colon cancer, pancreas cancer and prostate cancer.
35. A composition according to claim 33 or 34 where the vaccine elicits the production in
 10 the vaccinated subject of effector T-cells having a cytotoxic effect against the cancer cells.
36. A composition for ex vivo or in situ diagnosis of the presence in a cancer patient of survivin reactive T-cells among PBLs or in tumor tissue, the composition comprising a peptide according to claim 1.
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37. A diagnostic kit for ex vivo or in situ diagnosis of the presence in a cancer patient of survivin reactive T-cells among PBLs or in tumour tissue comprising a peptide according to claim 1.
- 20 38. A complex of a peptide according to claims 1 and a Class I HLA molecule or a fragment of such molecule.
39. A complex according to claim 38 which is monomeric.
- 25 40. A complex according to claim 38 which is multimeric.
41. A method of detecting in a cancer patient the presence of survivin reactive T-cells, the method comprising contacting a tumour tissue or a blood sample with a complex according to claim 38 and detecting binding of the complex to the tissue or the blood cells.
- 30 42. A molecule that is capable of binding specifically to a peptide according to claims 1.
43. A molecule according to claim 36 which is an antibody or a fragment hereof.
- 35 44. A molecule that is capable of blocking the binding of a molecule according to claim 42 or 43.
45. A method of treating a cancer disease, the method comprising administering to a patient suffering from the disease an effective amount of the composition according to claim
 40 25, a molecule according to claim 42 or a molecule according to claim 44.
46. A method according to claim 45 wherein the disease to be treated is a cancer disease where survivin is expressed.

47. A method according to claim 46 wherein the cancer disease is selected from the group consisting of a haematopoietic malignancy including chronic lymphatic leukemia and chronic myeloid leukemia, melanoma, breast cancer, cervix cancer, ovary cancer, lung cancer, colon cancer, pancreas cancer and prostate cancer.

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48. A method according to claim 45, which is combined with a further treatment.

49. A method according to claim 48 wherein the further treatment is radiotherapy or chemotherapy.

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